Efficient analysis of highly complex nuclear magnetic resonance spectra of flexible solutes in ordered liquids by using molecular dynamics

Weber, A.C.J.; Pizzirusso, A.; Muccioli, L.; Zannoni, C.; Meerts, W.L.; de Lange, C.A.; Burnell, E.E.

published in
Journal of Chemical Physics
2012

DOI (link to publisher)
10.1063/1.4705271

document version
Publisher's PDF, also known as Version of record

Efficient analysis of highly complex nuclear magnetic resonance spectra of flexible solutes in ordered liquids by using molecular dynamics

Adrian C. J. Weber, Antonio Pizzirusso, Luca Muccioli, Claudio Zannoni, W. Leo Meerts et al.

Citation: J. Chem. Phys. **136**, 174506 (2012); doi: 10.1063/1.4705271
View online: http://dx.doi.org/10.1063/1.4705271
View Table of Contents: http://jcp.aip.org/resource/1/JCPSA6/v136/i17
Published by the American Institute of Physics.

Efficient analysis of highly complex nuclear magnetic resonance spectra of flexible solutes in ordered liquids by using molecular dynamics

Adrian C. J. Weber,[1,a)] Antonio Pizzirusso,[2,b)] Luca Muccioli,[2,c)] Claudio Zannoni,[2,d)] W. Leo Meerts,[3,e)] Cornelis A. de Lange,[4,f)] and E. Elliott Burnell[1,g)]
[1]*Chemistry Department, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia V6T 1Z1, Canada*
[2]*Dipartimento di Chimica Fisica ed Inorganica, Università di Bologna, viale Risorgimento 4, 40136 Bologna, Italy*
[3]*Radboud University Nijmegen, Institute for Molecules and Materials, Heyendaalseweg 135, NL-6525 AJ Nijmegen, The Netherlands and Department of Physical Chemistry, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands*
[4]*Atomic, Molecular and Laser Physics, Vrije Universiteit, De Boelelaan 1081, 1081 HV Amsterdam, The Netherlands*

(Received 18 January 2012; accepted 5 April 2012; published online 3 May 2012)

The NMR spectra of *n*-pentane as solute in the liquid crystal 5CB are measured at several temperatures in the nematic phase. Atomistic molecular dynamics simulations of this system are carried out to predict the dipolar couplings of the orientationally ordered pentane, and the spectra predicted from these simulations are compared with the NMR experimental ones. The simulation predictions provide an excellent starting point for analysis of the experimental NMR spectra using the covariance matrix adaptation evolutionary strategy. This shows both the power of atomistic simulations for aiding spectral analysis and the success of atomistic molecular dynamics in modeling these anisotropic systems. © *2012 American Institute of Physics*. [http://dx.doi.org/10.1063/1.4705271]

I. INTRODUCTION

In general, NMR is a widely applicable and reliable method for the investigation of liquid crystals.[1] ^{1}H NMR is arguably the best technique for studying conformational statistics for solutes in liquid crystals and of liquid crystals themselves. Since the pioneering work of Saupe and Englert,[2] the NMR study of solutes dissolved in liquid-crystal solvents has attracted much attention. Initially most of the research carried out focused on properties of the solute. Since direct dipolar couplings are usually the dominant features in the observed NMR spectra, information on solute geometries in a liquid environment was obtained, especially on the relatively small solutes whose NMR spectra could be analyzed without too much difficulty. In addition, anisotropic contributions to the chemical shielding and the indirect spin-spin couplings, as well as quadrupolar couplings, in particular for deuterons, have been a rich source of information.[3–9]

In addition to the properties of solutes, appreciable attention has been focused on the interaction mechanisms in the liquid state that determine the observed average degree of solute orientational order. In this context, the use of small, very well characterized probe molecules has been crucial. These studies have led to a number of important insights.

The use of small probe molecules has provided an enormous stimulus in developing a basic understanding of the various mechanisms that are at the root of the orientational ordering process. A key discovery that has provided a breakthrough in understanding the mechanisms causing solute orientational order was that of zero-electric-field gradient "magic mixtures".[10] It has been shown that the solute orientational order in well-chosen liquid-crystal mixtures can be described by just a single mechanism that solely depends on solute size and shape. Moreover, the orientational order tensor can be modeled adequately by employing relatively simple phenomenological ideas. Many such models have been developed and most of them perform reasonably well.[8,11]

For normal liquid-crystal solvents, in addition to the size-and-shape contribution, a second mechanism is found to be important. This involves an interaction between the solute molecular quadrupole moment and the average electric field gradient present in the nematic phase.[12–14] This realization has led to the concept of "magic solutes", molecules that possess relatively small electrostatic moments. For such solutes the second contribution to the orientational degree of order then vanishes, and the single size-and-shape mechanism remains. The saturated alkanes (C_nH_{2n+2}) are a case in point.

The liquid-crystal NMR method discussed so far was not as widely applicable as one should wish. The complexity of ^{1}H spectral analysis grows very rapidly with the number of coupled spins. Because of the complexity of the NMR spectra of orientationally ordered solutes with more than eight nuclear spins $I = 1/2$, analyzing spectra of larger solutes became a major undertaking. The NMR spectrum of *n*-butane

a)Electronic mail: adri@chem.ubc.ca. Present address: Chemistry Department, Brandon University, Brandon, Manitoba, Canada.
b)Electronic mail: antonio.pizzirusso80@gmail.com.
c)Electronic mail: luca.muccioli@unibo.it.
d)Electronic mail: claudio.zannoni@unibo.it.
e)Electronic mail: leo.meerts@science.ru.nl. URL: http://www.leomeerts.nl.
f)Electronic mail: c.a.de.lange@vu.nl.
g)Electronic mail: elliott.burnell@ubc.ca.

could only be solved when time-consuming multiple quantum methods that required much expertise were employed.[15] Other methods, based at least in part on isotopic substitution, have also been used for studying longer alkanes[16] but, although valued for the wealth of conformational information they provide,[17,18] they have not found widespread use. An analysis using conventional methods of the NMR spectrum of *n*-pentane in a nematic phase (having of order 20 000 transitions) has not been reported. It seemed that a practical limit had been reached that could not be easily overcome with techniques available at that point. Recently a novel method to analyze complex NMR spectra of solutes in nematic liquid crystals has been introduced. The covariance matrix adaptation evolutionary strategy (CMA-ES) (Refs. 19 and 20) was found to be an invaluable tool for the analysis of NMR spectra of solutes with many spins in anisotropic environments.[21]

Evolution strategies such as CMA-ES are optimizers that are inspired by reproduction and natural selection in nature. While classical genetic algorithms aim to find a solution in the parameter space by randomly combining information from a set of trial solutions, the CMA-ES algorithm can sense in which direction the quality of a fit increases. In the first step, the CMA-ES algorithm generates trial solutions (offspring) by using a random distribution around some starting point (parent) each consisting of the complete parameter set which is necessary to simulate the spectrum. Offspring with higher fitness than the parent are kept and used to compute the next generation.

The CMA-ES algorithm makes use of the parameter correlation matrix for successive changes in the parents (mutations). This means that if for some parameter a parent has evolved in the same direction for several generations, resulting in a positive correlation, the most likely solution is assumed to be further in that direction and the next parameter mutation will be larger. Correspondingly, two anticorrelated mutations will lead to a smaller mutation. Compared to classical genetic algorithms, this procedure has been shown to lead to faster convergence of the parameters.[22,23]

The CMA-ES method has been shown to be an extremely useful novel tool for spectral analysis, to the extent that NMR spectral analysis has now become routine and is no longer the bottleneck in studies of this type. This development has important implications. We can now systematically study solutes that on the NMR time scale undergo conformational change. As the simplest example, recently an extensive temperature study of *n*-butane was performed in the liquid crystals 4-*n*-pentyl-4′-cyanobiphenyl (5CB) and Merck ZLI 1132 (1132).[24] For the first time a model-free NMR study of *n*-butane conformational statistics was performed successfully.[25] In addition, CMA-ES provided the first successful analysis of spectra of *n*-pentane in the liquid-crystal solvents 1132 and a magic mixture — albeit with starting parameters and ranges that were carefully chosen based on predictions for magic solutes from size and shape model calculations.[21]

The CMA-ES method is essentially a brute-force method that relies on recent developments in computer technology which have been geared towards the analysis of complex NMR spectra. In order for the method to reach convergence successfully within acceptable CPU-time, reasonable ranges for the dipolar couplings must be defined beforehand. So far these ranges were decided on by applying the above-mentioned phenomenological models and by incorporating a simple rotational isomeric state (RIS) approach for conformational changes. As is shown, e.g., in experimental studies of *n*-butane[26] and *n*-pentane,[21] the ranges for the dipolar couplings obtained in this way provide an adequate starting point for the evolutionary analysis procedure.

Recent advances in atomistic simulation methods have developed to the point where they can truly be considered as a complete, even if still limited in system size, computer experiment.[27–29] It is therefore tempting to make a detailed comparison between the temperature-dependent results that can be obtained from a liquid-crystal NMR experiment to date, and the predictions on the same physical system that can be made employing state-of-the-art atomistic simulation methods. In order to make such a comparison, we choose the benchmark system of *n*-pentane in the nematic phase of 5CB, studied as a function of temperature. The example of *n*-pentane in 5CB is illuminating in that both the solute and the nematic liquid crystal molecule undergo extensive conformational change which is reflected in both the experimental and simulated dipolar couplings.

The present paper will show that the agreement between the dipolar couplings derived from the NMR experiments and the simulations is remarkable. Moreover, the dipolar couplings obtained from the atomistic simulations are shown to provide an excellent starting point for the CMA-ES evolutionary fitting procedure. In this sense a brute-force simulation of the dipolar couplings in the *n*-pentane-5CB system is seen to agree very satisfactorily with the brute-force results of the CMA-ES fitting process. Although one may regret the fact that conventional analytical methods employed to solve very complex NMR spectra have now been superseded by novel approaches and have become obsolete, one cannot be blind to the enormous power and advances that modern computer technology is bringing to classical problems.

II. EXPERIMENTAL

Normal pentane and the orientational reference standard 1,3,5-trichlorobenzene (tcb) were dissolved in the nematic solvent 5CB to achieve a 4% and 1% mole fraction, respectively. Using a Bruker Inverse 400 MHz NMR spectrometer, ^{1}H NMR spectra were then obtained every 5° spanning a 25° range from 273.5 K to 298.5 K. The liquid-crystal background signal was removed using a cubic base spline giving the spectra shown in Fig. 1.

Starting with the results of the original pentane study where size and shape models were used to provide search limits for the dipolar couplings, a CMA-ES (Refs. 21 and 30) was used to extract the spectral parameters. The dipolar couplings obtained are reported in the left-hand columns of Table I. The atom labeling of pentane is shown in Fig. 2.

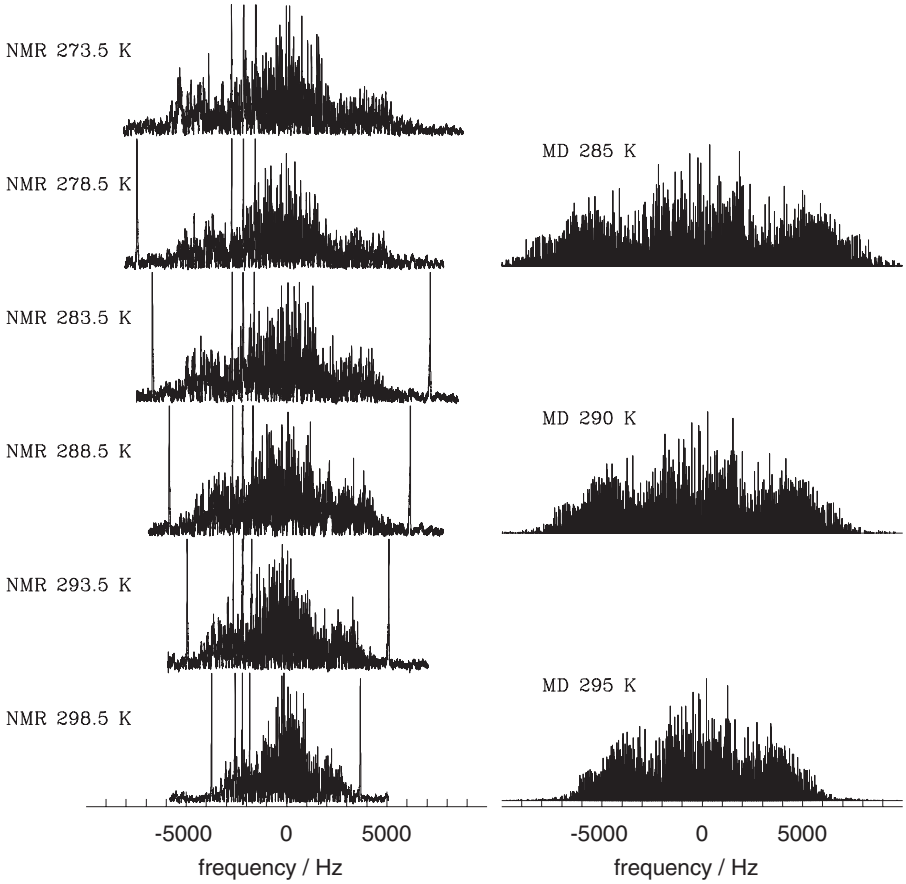

FIG. 1. Experimental (left) and calculated from MD simulations (right) spectra of pentane in 5CB. The intense lines in the outer regions of the NMR spectra arise from an unknown impurity in the 5CB, and the other three intense lines are the tcb triplet.

III. COMPUTER SIMULATION OF PENTANE IN A NEMATIC SOLVENT

A. Simulation details

Using the NAMD software,[31] we carried out molecular dynamics (MD) computer simulations on a sample of 1904 molecules of the solvent 5CB, 16 molecules of tcb, and 80 molecules of the solute *n*-pentane, for a total of 2000 molecules. This sample composition corresponds to that used in the experimental NMR study.

Pentane and tcb have been described with full atomistic detail, and the atomic charges[32] have been computed at their minimum energy geometry using the B3LYP density functional and the aug-cc-pVTZ basis set with the GAUSSIAN

TABLE I. Experimental ^{1}H-^{1}H dipolar couplings from NMR of *n*-pentane and tcb in 5CB as a function of temperature and averaged ^{1}H-^{1}H dipolar couplings (in Hz) from MD simulations. The numbers in round brackets are the errors in Hz in the last one or two digits. The numbers in square brackets indicate the ratios $\langle r_{ij}^{-3}\rangle/\langle r_{ij}\rangle^{-3}$ calculated from the simulations.

	^{1}H NMR experiments						MD simulations		
T (K)	273.5	278.5	283.5	288.5	293.5	298.5	285	290	295
D_{tcb}	–204.6(7)	–194.5(6)	–183.6(6)	–169.6(5)	–151.5(4)	–119.8(4)	–211 [1.001]	–189 [1.001]	–159 [1.001]
$D_{1,2}$	1043.92(4)	971.71(3)	898.93(3)	811.78(3)	707.77(2)	541.84(2)	1342 [1.007]	1121 [1.007]	926 [1.007]
$D_{1,4}$	–194.35(3)	–180.87(3)	–167.41(3)	–151.24(3)	–131.95(2)	–101.20(3)	–256 [1.066]	–213 [1.067]	–177 [1.067]
$D_{1,6}$	–636.35(3)	–591.11(2)	–545.69(3)	–491.68(2)	–427.74(2)	–326.65(2)	–793 [1.200]	–661 [1.201]	–544 [1.201]
$D_{1,8}$	–318.13(3)	–299.44(3)	–279.74(3)	–255.17(3)	–224.58(2)	–173.48(3)	–322 [1.268]	–274 [1.273]	–228 [1.282]
$D_{1,10}$	–162.04(3)	–152.17(3)	–141.92(3)	–129.30(3)	–113.64(2)	–87.72(2)	–176 [1.115]	–149 [1.116]	–123 [1.120]
$D_{4,5}$	2377.50(6)	2217.07(6)	2054.41(6)	1859.09(5)	1624.63(4)	1247.77(4)	2905 [1.007]	2433 [1.007]	2011 [1.007]
$D_{4,6}$	–4.88(10)	–9.19(9)	–12.20(9)	–14.72(7)	–16.22(5)	–15.43(6)	19 [1.040]	–5 [1.041]	–1 [1.042]
$D_{4,7}$	72.92(10)	66.26(8)	59.93(8)	52.49(7)	44.63(5)	33.24(6)	128 [1.048]	105 [1.049]	83 [1.050]
$D_{4,8}$	–972.88(8)	–896.34(7)	–821.30(7)	–734.13(6)	–633.80(5)	–480.15(5)	–1264 [1.171]	–1042 [1.173]	–848 [1.177]
$D_{4,9}$	–595.24(8)	–556.33(7)	–516.62(7)	–468.29(6)	–409.59(5)	–314.58(5)	–686 [1.149]	–583 [1.153]	–482 [1.157]
$D_{6,7}$	2489.57(10)	2324.48(9)	2156.57(10)	1953.87(8)	1709.98(6)	1315.52(6)	2993 [1.007]	2517 [1.007]	2078 [1.007]

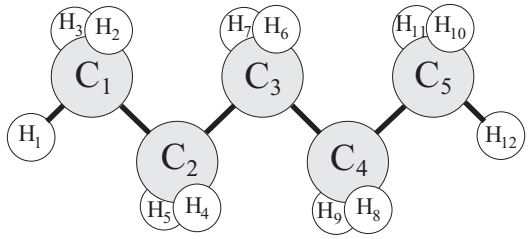

FIG. 2. Labelling scheme used for nuclei in *n*-pentane.

package.[33] The other force field parameters for pentane were gathered from the AMBER-OPLS force field, including the torsional potential for the rotation of methyl and methylene groups.[34,35] The 5CB solvent molecules have been instead described at the united atoms level of detail, using a force field that reproduces the experimental nematic-isotropic transition temperature and a number of other observables for *n*CB ($n = 4 - 8$).[27] The Lennard-Jones non-bonded interactions were evaluated using a cutoff of 12 Å, while long-range electrostatic ones were calculated with the particle mesh Ewald method and a mesh size of 1.2 Å. NPT MD simulations were run at atmospheric pressure and scanning the temperature interval $T = 285$–310 K with steps of 5 K. We used a timestep of 1 fs, a typical MD equilibration time ranging from 30 to 50 ns and a production time of 30 ns for all temperatures, a time long enough to exceed, for these low molecular mass solutes, their typical reorientational and conformational relaxation times.[36,37] The time window is also adequate for observing possible fluctuation of the 5CB nematic order parameter, as shown in Ref. 27. We have already validated this simulation protocol by studying the ordering effect of 5CB on simple rigid oblate and prolate solutes and comparing the MD predictions with experimental results and mean field theories.[38]

B. Temperature dependence of order parameters

In order to determine $\langle P_2 \rangle$ from the MD trajectories we used the instantaneous director frame $\hat{n}(t)$ for the configuration at time t for computing the angle β between the phase director and the reference axis $\hat{u}_i$ of the molecule i, and taking, for the selected species, an average over all the N molecules in the sample, followed by an average over all times t_i

$$\langle P_2 \rangle = \frac{1}{TN} \sum_{i=1}^{T} \sum_{j=1}^{N} P_2(\hat{u}_j(t_i) \cdot \hat{n}(t_i)). \tag{1}$$

The reference axis for 5CB and pentane is taken to be the instantaneous principal axis of the inertia tensor of the molecule corresponding to the lowest eigenvalue (other possible choices will be discussed later). The results are reported in Table II and Fig. 3 where we see that the first general effect of adding pentane is that of lowering the solvent $\langle P_2 \rangle$ at a given temperature through shifting the simulated nematic-isotropic transition temperature from the pure solvent value of ≈310 K (Ref. 27) to $T \approx 300$ K.

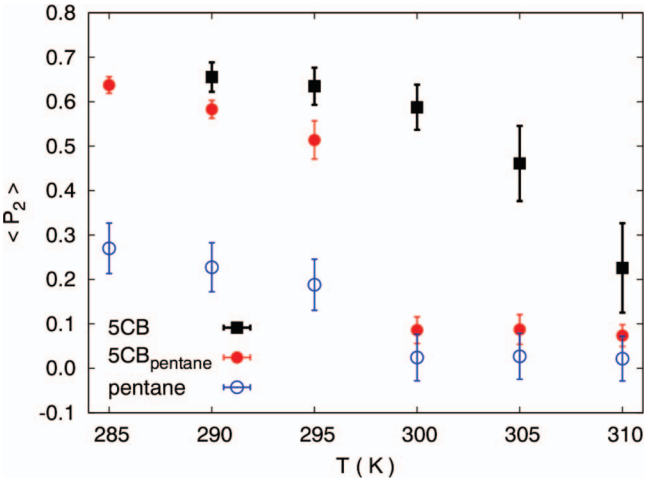

FIG. 3. Comparison of simulated 5CB average order parameter values both in the presence of pentane (red circles, this work) and for a sample of 250 molecules of bulk 5CB (black squares, Ref. 27) as a function of temperature. The order parameter for pentane is also reported (empty blue circles).

The description of the orientational order in a system consisting of flexible molecules, such as pentane, cannot be defined completely using only the order parameter of one inertia axis; the required additional quantities are the order parameters for every fragment.[39] For pentane we used two ways for calculating order parameters of the fragments chosen. The first approach involves subdividing the flexible molecules into methyl ($-CH_3$) and methylene ($-CH_2$ $-$) units. For each fragment we have taken the average order parameter value with respect to the director $\hat{n}(t)$ of the vectors r_{CH} defined by a particular carbon atom and its directly bonded hydrogen atoms, shown in Fig. 4. We note that, as expected, the absolute value of the orientational order parameter for every unit decreases as a function of temperature. Also, the methylene fragments have a higher order parameter absolute value than the methyls. The second approach involves taking the order parameter for every carbon-carbon bond vector. The results are displayed in Fig. 5. In this case the different alignments with respect to the mesophase director for the pentane units are also visible, but less pronounced.

C. Dipolar couplings

From simulation we can obtain the dipolar couplings using the relation

$$D_{ij} = -\frac{\mu_0}{8\pi^2} \gamma_i \gamma_j \hbar \left\langle \frac{P_2(\cos\theta_{ij})}{r_{ij}^3} \right\rangle, \tag{2}$$

TABLE II. Order parameters of pentane (solute) and of 5CB (liquid crystal solvent) in the presence of solute, obtained by MD simulation as a function of temperature.

T / K	285	290	295	300	305	310
5CB	0.64 ± 0.02	0.58 ± 0.02	0.51 ± 0.04	0.09 ± 0.03	0.09 ± 0.03	0.07 ± 0.02
pentane	0.27 ± 0.06	0.23 ± 0.05	0.19 ± 0.06	0.02 ± 0.05	0.03 ± 0.05	0.02 ± 0.05

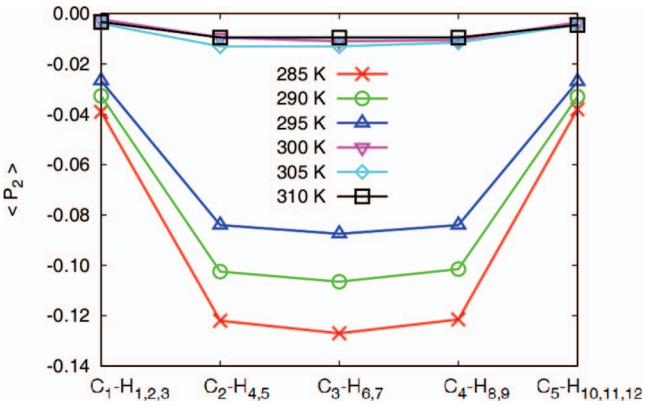

FIG. 4. Order parameter from MD simulation as function of C–H bond position at all the studied temperatures.

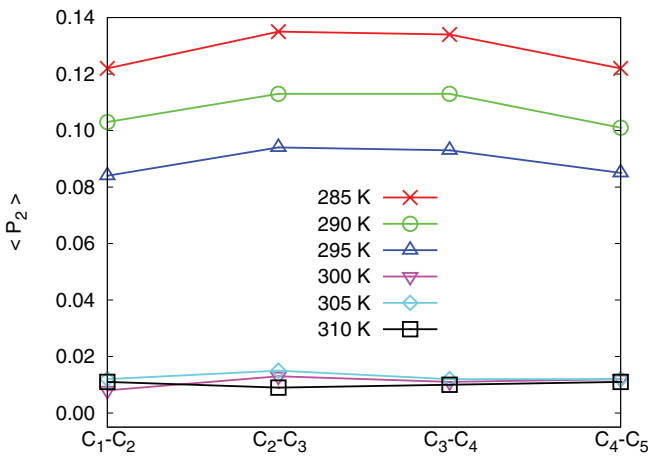

FIG. 5. Order parameters of C–C bonds from MD simulations at all the studied temperatures.

where r_{ij} is the internuclear distance and θ_{ij} describes the orientation with respect to the magnetic field B (in our case, coincident with the instantaneous phase director); $\mu_0 = 4\pi \times 10^{-7}$ $T^2J^{-1}m^3$ is the magnetic permeability in vacuum; $\gamma_i = g_i\mu_N/\hbar$ is the nuclear gyromagnetic ratio expressed in radians. The values of the ^{1}H-^{1}H dipolar couplings obtained from the simulations are reported in the last three columns of Table I, while those for the directly bonded ^{13}C-^{1}H and ^{13}C-^{13}C dipolar couplings are reported in Table III. As expected, all couplings get smaller in absolute value as temperature increases. All of them have the correct sign, magnitude, and slope with respect to temperature, with the exception of $D_{H_4H_6}$ which, however, is very close to zero.

We remark that, besides torsions, also bond lengths and angles are not fixed in the simulation so that the simulated couplings reported allow for vibrational and torsional averaging. In Table I we have also estimated the importance of vibrational and librational motions for the ^{1}H-^{1}H dipolar couplings by computing for each of them the ratio between the inverse of the average internuclear distance cubed $\langle r_{ij}\rangle^{-3}$ and the average inverse cube of the internuclear distance $\langle r_{ij}^{-3}\rangle$ that is more closely related to Eq. (2). These ratios are all equal to one for a perfectly rigid molecule, while here we find deviations that change from pair to pair and with temperature, ranging from 0.1% to about 28%. It is not surprising that the highest ratios are registered for pairs of hydrogens belonging to different methylene or methyl groups.

IV. COMPARISON BETWEEN NMR EXPERIMENTAL AND MD SIMULATION DIPOLAR COUPLINGS

Now we compare the dipolar couplings obtained from simulations with the experimental ones obtained from fitting the NMR spectra (Table I). We notice that at a given temperature the dipolar couplings simulated within the nematic temperature range of 5CB are systematically higher than the experimental ones, indicating that the solute has lower orientational order than predicted by the simulations. In both cases the nematic–isotropic transition temperature of the solution is lowered to approximately 300 K, and hence comparison at the same real temperature corresponds to the same reduced temperature. While we have no explanation for why the solute has lower orientational order than calculated, we do note that comparison between NMR and MD results at different temperatures is interesting. For example, when we compare the NMR results for 283.5 K with the MD for 295 K, we note remarkable agreement between NMR and MD couplings, with the magnitudes of some MD couplings being larger and some smaller. The RMS difference between MD and NMR couplings is 45 Hz. This number is considerably larger than the 7 Hz obtained when fitting pentane dipolar couplings to models and adjusting model parameters, *trans* − *gauche* energy parameters and the CCH angle. However, the agreement is phenomenal when considering that in this case there are no adjustable parameters — the only "fitting" here is to compare simulated and experimental spectra at different temperatures. This indeed confirms the success of the MD in describing the actual orientational ordering situation of the pentane solute in the 5CB nematic phase.

An important general question here is whether or not the MD couplings can be used as starting parameters for a CMA-ES fit to the experimental NMR spectra. To investigate this possibility and to develop a possible strategy, we proceed as follows. First, we compare visually the NMR experimental

TABLE III. Mean ^{13}C–^{1}H (carbon-geminal hydrogen) and ^{13}C–^{13}C dipolar couplings (in Hz) from MD simulations.

T/K	$D_{C_1H_{1,2,3}} = D_{C_5H_{10,11,12}}$	$D_{C_2H_{4,5}} = D_{C_4H_{8,9}}$	$D_{C_3H_{6,7}}$	$D_{C_1C_2} = D_{C_4C_5}$	$D_{C_2C_3} = D_{C_3C_4}$
285	901	2830	2943	–255	–278
290	754	2370	2471	–213	–234
295	624	1954	2041	–176	–193

with the MD-predicted spectra in Fig. 1. Although a detailed comparison is clearly impossible, we tentatively search for similar experimental and simulated spectral widths. In this case, we choose the NMR 283.5 K and the MD 295 K spectra for the trial. We now wish to define reasonable ranges for the dipolar couplings required as starting values for the CMA-ES procedure. For larger dipolar couplings, we take the MD value and apply a range of ±15%. Because smaller couplings may arise as a result of large positive and large negative contributions (see for example Table 1 of Ref. 21 where some dipolar couplings are predicted to change sign with conformation), for smaller couplings we adopt the MD values with a range of ±50 Hz. When we input these initial dipolar couplings obtained from MD and their estimated ranges into the CMA-ES programme, quick convergence is reached. An excellent fit to the experimental spectrum is obtained, and the results are reported in Table I. This dramatic result demonstrates the power of combining MD atomistic simulations and CMA-ES for assigning the NMR spectra of orientationally ordered solutes in anisotropic environments, even for solutes that show very complex NMR spectra with over 20 000 transitions.

It is important to note that MD simulations will always provide starting values accurate enough to start a CMA-ES fit of the experimental spectrum using relatively narrow search ranges. This cannot be said for other methods for which large search ranges must be employed in order to cover the possibility that some couplings may well deviate widely from the prediction. For example, in our first pentane paper[21] we have a table of D_{ij} for the four different conformers, and from that table it should be obvious that changing the conformer mix leads to vastly different D_{ij}, including sign changes.

One important point remains to be made. In previous liquid-crystal NMR studies on the flexible solutes *n*-butane and *n*-pentane that undergo extensive conformational change, the dipolar couplings analyzed with the help of the CMA-ES approach could be reasonably interpreted in terms of relatively simple models. To start with, the observed dipolar couplings had to be corrected for the effects of the notorious interaction between vibrational and reorientational motion.[40] These corrections are not easy to make and not always unambiguous. In order to account for conformational change, a RIS model was employed, and energy differences between *trans* and *gauche* conformations were introduced. Although no exact correspondence between experimental dipolar couplings and those recalculated with such models could be obtained for *n*-butane and *n*-pentane, this approach has an important advantage. The physical parameters resulting from the modeling, e.g., *trans-gauche* energy differences, can be compared to the results of other experimental methods or *ab initio* molecular structure calculations. Such comparisons can be of great help in stimulating an intuitive insight.

In the MD atomistic simulations, all the internal motions of both solvent and solute molecules are accounted for by introducing appropriate force fields. In this sense all the effects of internal molecular motion, such as vibration-reorientation interaction and conformational change, are taken into account without further ado. The disadvantage is that only the definitive dipolar couplings are obtained from the simulations, but the physical parameters that can be compared to those observed with other methods are not obtained explicitly.

V. CONCLUSIONS

Atomistic MD simulations of 5CB were carried out in the presence of the solutes *n*-pentane and 1,3,5 trichlorobenzene. These simulations correctly predict the shift of the nematic-isotropic transition to a lower temperature of about 299.5 K on introducing the solutes. The essential results arising from these simulations are dipolar couplings that can then be compared to experiment. The MD couplings for a given temperature are larger in magnitude than the NMR ones, probably because the model for pentane is slightly more rigid than in reality. When couplings for different temperatures are compared (for example NMR at 283.5 K with MD at 295 K), the agreement between experiment and simulation is excellent. This agreement indicates that the simulations do indeed encapsulate the correct physical picture of this orientationally ordered system.

The CMA-ES technique can in principle be used for much larger solutes with many coupled spins or for solutes for which size-and-shape phenomenological models for the prediction of orientational order may be inadequate. This is especially true for solvent-solute systems that deviate significantly from the relatively simple "magic mixture" or "magic solute" cases where the one-mechanism size-and-shape approach is expected to be inadequate. Under such conditions it is clearly essential to generate a good starting point for the analysis of complex NMR spectra.

In this paper we demonstrate that state-of-the-art atomistic MD simulations are capable of generating dipolar couplings for orientationally ordered solutes that can be used as a starting point for the detailed CMA-ES procedure (as long as one uses the MD results that lead to a simulated NMR spectrum with a total spectral width comparable to that of the experimental spectrum). These high-quality simulations are applied to the most challenging solvent-solute system analyzed to date, viz. *n*-pentane dissolved in 5CB. The fact that orientationally ordered *n*-pentane shows a ^{1}H NMR spectrum with more than 20 000 transitions and the success of the combined MD/CMA-ES procedure is an impressive demonstration indeed. The fact that atomistic MD simulations are capable of providing adequate starting values for solute dipolar couplings to analyze the actual solute NMR spectra in a system as complex as *n*-pentane in 5CB bodes well for the future. In situations where the phenomenological size-and-shape models fail because orientational order depends on more than one orientational mechanism, MD simulations are now likely to present the key to a solution. Also, the ultimate aim to eventually provide simulations that yield the reduced dipolar couplings that have become important for protein structure determination by NMR has become less elusive than before.

ACKNOWLEDGMENTS

E.E.B. acknowledges financial support from the Natural Sciences and Engineering Research Council of Canada. A.P., L.M., and C.Z. thank MIUR for funding this research through

the PRIN grant "Novel ordered systems for high response molecular devices".

[1]J. P. Jokisaari, A. M. Kantola, J. A. Lounila, and L. Petri Ingman, Phys. Rev. Lett. **106**, 017801 (2011).
[2]A. Saupe and G. Englert, Phys. Rev. Lett. **11**, 462 (1963).
[3]A. D. Buckingham and K. A. McLauchlan, Prog. NMR Spectrosc. **2**, 63 (1967).
[4]P. Diehl, and C. L. Khetrapal, *NMR Basic Principles and Progress* (Springer-Verlag, Berlin, 1969), Vol. 1, p. 1.
[5]J. W. Emsley and J. C. Lindon, *NMR Spectroscopy using Liquid Crystal Solvents* (Pergamon, Oxford, 1975).
[6]J. Lounila and J. Jokisaari, Prog. NMR Spectrosc. **15**, 249 (1982).
[7]R. Y. Dong, *Nuclear Magnetic Resonance of Liquid Crystals*, 1st ed. (Springer-Verlag, New York, 1994).
[8]*NMR of Ordered Liquids*, edited by E. E. Burnell and C. A. de Lange (Kluwer Academic, Dordrecht, The Netherlands, 2003).
[9]R. Y. Dong, *Nuclear Magnetic Resonance Spectroscopy of Liquid Crystals*, edited by R. Y. Dong (World Scientific, Singapore, 2009).
[10]J. B. S. Barnhoorn, C. A. de Lange, and E. E. Burnell, Liq. Cryst. **13**, 319 (1993).
[11]G. Celebre, M. Concistré, G. De Luca, M. Longeri, and G. Pileio, ChemPhysChem. **7**, 1930 (2006).
[12]E. E. Burnell and C. A. de Lange, Chem. Rev. **98**, 2359 (1998) and references therein.
[13]G. Celebre and A. Ionescu, J. Phys. Chem. B. **114**, 228 (2010).
[14]G. Celebre and A. Ionescu, J. Phys. Chem. B. **114**, 235 (2010).
[15]J. M. Polson and E. E. Burnell, J. Chem. Phys. **103**, 6891 (1995).
[16]M. E. Rosen, S. P. Rucker, C. Schmidt, and A. Pines, J. Phys. Chem. **97**, 3858 (1993).
[17]D. J. Photinos, E. T. Samulski, and H. Toriumi, J. Phys. Chem. **94**, 4688 (1990).
[18]R. Berardi, F. Spinozzi, and C. Zannoni, Chem. Phys. Lett. **260**, 633 (1996).
[19]A. Ostermeier, A. Gawelczyk, and N. Hansen, *Lecture Notes in Computer Science: Parallel Problem Solving from Nature (PPSN III)* (Springer, 1994), p. 189.
[20]N. Hansen and A. Ostermeier, Evol. Comput. **9**, 159 (2001).
[21]W. L. Meerts, C. A. de Lange, A. C. J. Weber, and E. E. Burnell, J. Chem. Phys. **130**, 044504 (2009) and references therein.
[22]I. Kalkman, C. Vu, M. Schmitt, and W. L. Meerts, ChemPhysChem. **9**, 1788 (2008).
[23]M. Schmitt, L. Biemann, W. L. Meerts, and K. Kleinermanns, J. Mol Spectrosc. **257**, 74 (2009).
[24]A. C. J. Weber and E. E. Burnell, Chem. Phys. Lett. **506**, 196 (2011). (Note that the CCH angle increase reported in this paper is actually the CCH angle decrease).
[25]E. E. Burnell, A. C. J. Weber, C. A. de Lange, W. L. Meerts, and R. Y. Dong, J. Chem. Phys. **135**, 234506 (2011).
[26]A. C. J. Weber, C. A. de Lange, W. L. Meerts, and E. E. Burnell, Chem. Phys. Lett. **496**, 257 (2010).
[27]G. Tiberio, L. Muccioli, R. Berardi, and C. Zannoni, ChemPhysChem. **10**, 125 (2009).
[28]T. A. Papadopoulos, L. Muccioli, S. Athanasopoulos, A. B. Walker, C. Zannoni, and D. Beljonne, Chem. Sci. **2**, 1025 (2011).
[29]A. Pizzirusso, R. Berardi, L. Muccioli, M. Ricci, and C. Zannoni, Chem. Sci. **3**, 573 (2012).
[30]W. L. Meerts and M. Schmitt, Int. Rev. Phys. Chem. **25**, 353 (2006).
[31]J. C. Phillips, R. Braun, W. Wang, J. Gumbart, E. Tajkhorshid, E. Villa, C. Chipot, R. D. Skeel, L. Kale, and K. Schulten, J. Comput. Chem. **26**, 1781 (2005).
[32]B. H. Besler, K. M. Merz, Jr., and P. A. Kollman, J. Comput. Chem. **11**, 431 (1990).
[33]M. J. Frisch, G. W. Trucks, H. B. Schlegel *et al.*, GAUSSIAN 03, Revision C.02., Gaussian, Inc., Wallingford, CT, 2004.
[34]W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz, D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell, and P. A. Kollman, J. Am. Chem. Soc. **117**, 5179 (1995).
[35]J. Wang, P. Cieplak, and P. A. Kollman, J. Comput. Chem. **21**, 1049 (2000).
[36]Y. Zhang, R. M. Venable, and R. W. Pastor, J. Phys. Chem. **100**, 2652 (1996).
[37]M. Mondello and G. S. Grest, J. Chem. Phys. **106**, 9327 (1997).
[38]A. Pizzirusso, M. B. Di Cicco, G. Tiberio, L. Muccioli, R. Berardi, and C. Zannoni, J. Phys. Chem. B **116**, 3760 (2012).
[39]C. Zannoni, "An internal order parameter formalism for non-rigid molecules," in *Nuclear Magnetic Resonance of Liquid Crystals*, edited by J. W. Emsley (Reidel, Dordrecht, 1984), pp. 35–52.
[40]C. A. de Lange, W. L. Meerts, A. C. J. Weber, and E. E. Burnell, J. Phys. Chem. A **114**, 5878 (2010).